THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ, on behalf of the CANTOS Trial Group. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind placebo-controlled trial. *Lancet* 2017; published online Aug 27. http://dx.doi.org/10.1016/S0140-6736(17)32247-X.

Supplemental Appendix

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Anti-Inflammatory Therapy with Canakinumab and Lung Cancer

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A. Lists of Investigators

Scientific Advisory Panel/Executive Committee : Paul Ridker (Chair), John Kastelein, Wolfgang Koenig, Jacques Genest, Robert J Glynn, Peter Libby, Tom Thuren (non-voting).

Steering Committee/Country Leads: Paul Ridker (Chair, USA), Alberto Lorenzatti (Argentina); Henry Krum*, John Varigos (Australia); Peter Siostrzonek (Austria); Peter Sinnaeve (Belgium), Francisco Fonseca, Jose Nicolau (Brazil); Nina Gotcheva (Bulgaria); Jacques Genest (Canada); Huo Yong (China); Miguel Urina-Triana (Colombia); Davor Milicic (Croatia); Renata Cifkova (Czech Republic); Riina Vettus (Estonia); Wolfgang Koenig, Stephan D Anker (Germany); Athanasios J Manolis (Greece); Fernando Wyss (Guatemala); Tamas Forster (Hungary); Axel Sigurdsson (Iceland); Prem Pais (India); Alessandro Fucili (Italy); Hisao Ogawa, Hiroaki Shimokawa (Japan); Irina Veze (Latvia); Birute Petrauskiene (Lithuania); Leon Salvador (Mexico); John Kastelein, Jan Hein Cornel (Netherlands); Tor Ole Klemsdal (Norway); Felix Medina (Peru); Andrzej Budaj (Poland); Luminita Vida-Simiti (Romania); Zhanna Kobalava (Russia); Petar Otasevic (Serbia); Daniel Pella (Slovakia); Mitja Lainscak (Slovenia); Ki-Bae Seung (South Korea); Patrick Commerford (South Africa); Mikael Dellborg (Sweden); Marc Donath (Switzerland); Juey-Jen Hwang (Taiwan); Hakan Kultursay (Turkey); Marcus Flather (United Kingdom), Christie Ballantyne, Seth Bilazarian, William Chang, Cara East, Brendan Everett, Les Forgosh, Robert Glynn, Barry Harris, Peter Libby, Monica Ligueros, Paul Ridker, Tom Thuren (USA). [* deceased]

Publications Committee: Paul Ridker (Chair), Peter Libby, Robert Glynn, Tom Thuren

Cardiovascular and Death Endpoint Adjudication Committee: Brendan Everett (Chair), Erin Bohula, Bindu Charmarthi, Susan Cheng, Sherry Chou, Jacqueline Danik, Graham McMahon, Bradley Maron, MingMing Ning, Benjamin Olenchock, Reena Pande, Todd Perlstein, Aruna Pradhan, Natalia Rost, Aneesh Singhal, Viviany Taqueti, Nancy Wei.

Malignancy Adjudication Committee: Howard Burris (Chair), Angela Cioffi, Anne Marie Dalseg, Nilanjan Ghosh, Julie Gralow, Tina Mayer, Hope Rugo.

Infection Adjudication Committee: Vance Fowler (Chair), Ajit P. Limaye (C-Chair), Sara Cosgrove, Donald Levine, Renato Lopes, John Scott.

Sponsor (Novartis) Global Clinical and Operational Support Team: Tom Thuren, Monica Ligueros, Robert Hilkert, Georgia Tamesby, Carolyn Mickel, Brian Manning, Julian Woelcke, Monique Tan, Sheryl

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Data and Safety Monitoring Board: Rory Collins (Chair), Kent Bailey, Roger Blumenthal, Helen Colhoun, Bernard Gersh, Robert J Glynn (non-voting).

B. Inclusion and Exclusion Criteria for CANTOS

Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.

2. Male, or Female of non-child-bearing potential

3. Age ≥ 18 years at Visit 1.

4. Documented spontaneous MI (diagnosed according to the universal MI criteria with or without evidence of ST segment elevation) at least 30 days before randomization. (1)

- Diagnosis of the qualifying MI should be based on medical history of clinical symptoms consistent with myocardial ischemia associated with elevation of cardiac biomarkers above the 99th percentile of the upper reference limit (preferably troponin) OR development of new pathological Q waves regardless of symptoms. For details, refer to the Universal Definition of MI (1).

- Please see below for documentation requirements.

a. Acute MI (hospitalization records): requires documentation of a rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) or above criteria diagnostic for MIAND evidence of myocardial ischemia as demonstrated by at least one of the following :

i. Symptoms of ischemia

ii. ECG changes indicative of new ischemia (new ST-T changes or new LBBB)

iii. Development of pathologic Q waves

iv. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

b. Prior MI (no hospital records for acute event available): requires documentation of any one of the following:

i. Development of pathological Q waves, with or without symptoms

ii. Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause

iii. Pathologic findings of a healed or healing MI

- Patients with MI resulting from PCI or CABG will not be eligible

5. Have an hsCRP ≥ 2 mg/L (collected less than 60 days prior to Visit 2 and performed at the central laboratory, which is a minimum of 28 days after qualifying MI or after any PCI performed separately from qualifying MI) on stable (at least 4 weeks) long term (cardiovascular) medications.

Exclusion criteria

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test

2. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they are

a. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone or partial or total hysterectomy, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

[For Croatia only]

[In Croatia, women who are < 50 years of age must have >2 years of amenorrhea or minimum of 1 year of amenorrhea with FSH levels of ≥40 IU determined on 2 or more occasions at least one month apart]

3. Any of the following concomitant conditions or diseases:

a. Planned coronary revascularization (PCI or CABG) or any other major surgical procedure.

b. Major non-cardiac surgical or major endoscopic procedure within the past 6 months prior to Visit 1

c. Multi-vessel CABG surgery within the past 3 years

d. Symptomatic patients with Class IV heart failure (HF) (New York Heart Association).

e. Uncontrolled hypertension (defined as an average SBP >160 mmHg or an average diastolic blood pressure (DBP) >100 mmHg at Visit 1. Patients are allowed to be re-evaluated, at the discretion of investigator for this criterion if anti-hypertensive therapy has been started or increased as a result of initial screening blood pressure above these limits (2).

f. Uncontrolled diabetes as defined by the investigator

g. Nephrotic syndrome or eGFR < 30 mL/min/1.73 m2 per MDRD formula or kidney transplant (regardless of renal function), at Visit 1

h. Known active or recurrent hepatic disorder (including cirrhosis, hepatitis B and hepatitis C (positive or indeterminate central laboratory results), or alanine aminotransferase/ aspartate aminotransferase (ALT/AST) levels > 3 times ULN or total bilirubin > 2 times ULN) at Visit 1

i. Prior malignancy other than basal cell skin carcinoma

4. A history of alcohol and/or substance abuse that could interfere with the conduct of the trial

5. History or evidence of tuberculosis (TB) (active or latent) infection or one of the risk factors for tuberculosis such as but not limited or exclusive to:

a. History of any of the following: residence in a congregate setting (e.g. jail or prison, homeless shelter, or chronic care facility), substance abuse (e.g. injection or non-injection) health-care workers with unprotected exposure to patients who are at high risk of TB or patients with TB disease before the identification and correct airborne precautions of the patient

b. Close contact (i.e. share the same air space in a household or other enclosed environment for a prolonged period (days or weeks, not minutes or hours)) with a person with active pulmonary TB disease within the last 12 months.

c. Evidence of TB infection (active or latent), at Visit 1, determined by purified protein derivative (PPD) skin test and/or QuantiFERON®-TB Gold (QFT-g) assay as defined by country guidelines.

i. If presence of TB (active or latent) is established then treatment (according to country guidelines for TB treatment or TB treatment with immunomodulating drugs) must have been initiated or completed prior to randomization per country guidelines.

ii. In the absence of country TB (active or latent) guidelines, the following has been demonstrated: TB has been treated adequately with antibiotics, cure can be demonstrated, and risk factors resulting in TB exposure and contracting TB have been removed (e.g. the patient does not live anymore in high TB exposure setting).

6. History of ongoing, chronic or recurrent infectious disease

7. Patients with suspected or proven immunocompromised state, including (a) those with evidence of Human Immunodeficiency Virus (HIV) infection; Patients on anti-retroviral therapy are excluded (b) those with any other medical condition which in the opinion of the investigator places the patient at unacceptable risk for participation in immunomodulatory therapy; or (c) those requiring systemic or local treatment with any immune modulating agent in doses with systemic effects e.g. high dose oral or intravenous steroids (> 20 mg prednisone orally daily for > 14 days, > 5 mg prednisone orally daily or equivalent dose of intravenous steroid) or high dose methotrexate (> 15 mg weekly). Topical, inhaled, local steroid use in doses that are not considered to cause systemic effects are permitted.

8. Live vaccinations within 3 months prior to the randomization visit or live vaccinations planned during the trial.

9. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.

10. Patients who have received an investigational drug or device within 30 days (inclusive) of Visit 1, or who are expected to participate in any other investigational drug or device study during the conduct of this trial, except for patients who have an investigational drug eluting stent (DES), provided that they have completed the DES trial. FDA/country-specific drug regulatory authority approved DES devices are permitted.

11. Any biologic drugs targeting the immune system (for example, TNF blockers, anakinra, rituximab, abatacept, tocilizumab)

12. Any life threatening condition with life expectancy < 5 years, other than vascular disease that might prevent the patient from completing the study

Determination of tuberculosis status

Determination of tuberculosis (active or latent) status, either by performing the PPD skin test or the QFT-g assay will be required before administration of study drug and should be performed as defined by

country guidelines. Patients need to have given written informed consent before any of these assessments are initiated. Patients who have had a negative PPD skin test or negative QFT-g assay performed within 30 days of screening (Visit 1) will not need repeat testing performed to determine eligibility. All other patients will need tuberculosis (active or latent) status determined at Visit 1.

Any significant findings will be recorded in the "Medical History" section of the eCRF as necessary.

Patients with either a positive PPD or positive or indeterminate QFT-g test may still participate in the study if

1. Treatment of tuberculosis (active or latent) (according to country guidelines) has been initiated or completed prior to randomization

or

2. Patients with a history of TB who were treated must demonstrate that treatment has been received and further work up (according to country practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis.

or

3. The repeat QFT-g test is negative in patients with an indeterminate QFT-g result at Visit 1.

PPD skin test

A PPD skin test may be initiated to evaluate for an occult infection with TB. The test dose is bioequivalent to 5 tuberculin units (or as according to local standard practice) of standard PPD usually injected intradermally into the volar surface of the forearm. The injection site will be cleansed and the PPD extract will then be injected into the most superficial layer under the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

A reaction will be measured in millimeters of indurations (hard swelling) after 48h – 72h. A PPD skin induration > 5 mm is interpreted as positive result. This will determine whether the patients have had a significant reaction to the PPD skin test. In case of a positive PPD skin test, the patient may be further screened for latent TB infection by performing the QFT-g test.

The investigator will either obtain PPD skin tests on his own and be reimbursed by Novartis for its cost or be supplied with them by the Novartis affiliate, depending on the local Novartis policy.

QuantiFERON-TB Gold Assay

A QuantiFERON®-TB Gold (QFT-g) assay may be performed to assess the TB (active or latent) status at baseline on patients as needed.

This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous Bacillus Calmette-Guérin (BCG) vaccination or exposure to other Mycobacteria species. This test, in contrast to the PPD skin test, is also insensitive to a booster effect since the patient is not exposed to the vaccine. The assay measures the production of interferon-gamma and puts it into relation to a negative and a positive control sample.

C. Supplemental Table S1. Baseline clinical characteristics of CANTOS participants by treatment status.

Characteristic	Placebo (N=3344)	Canakinumab Dose (SC q 3 months) 50mg (N=2170)	150mg (N=2284)	300mg (N=2263)	All Doses (N=6717)
Mean age (yr)	61.1	61.1	61.2	61.1	61.1
Female sex (%)	25.9	24.9	25.2	26.8	25.6
Smoking Status (%)					
Current smoking	22.9	24.5	23.4	23.7	23.8
Past smoking	48.4	47.6	46.5	46.0	46.7
Never smoker	28.7	27.9	30.2	30.4	29.5
Body mass index (kg/m^2)	29.7	29.9	29.8	29.8	29.9
Waist circumference (cm)	104.0	105.0	104.0	104.1	104.2
Alcohol use (%, >1/day)	4.1	3.9	3.5	4.2	3.9
Hypertension (%)	79.1	80.7	79.4	79.5	79.9
Diabetes (%)	39.9	39.4	41.8	39.2	40.1
Daily exercise (%)	17.5	16.8	17.1	16.8	16.9
Qualifying myocardial infarction (%)					
STEMI	54.0	56.7	53.9	53.6	54.7
Non-STEMI	33.9	32.7	34.2	33.6	33.5
Unknown/missing	12.1	10.6	11.9	12.8	11.8
History of PCI (%)	65.6	67.0	68.1	66.7	67.3
History of CABG (%)	14.0	13.9	14.2	14.0	14.0
History of congestive heart failure (%)	21.6	20.8	20.9	23.1	21.6
Lipid lowering therapy (%)	93.7	94.0	92.7	93.5	93.3
Renin-angiotensin inhibitors (%)	79.8	79.3	79.8	79.6	79.3
Anti-ischemia agents* (%)	92.1	91.0	91.2	91.1	91.0
hsCRP (mg/L)	4.1	4.25	4.25	4.15	4.2
Il-6 (ng/L)	2.61	2.53	2.56	2.59	2.56
Total cholesterol (mg/dL)	160.5	159.0	159.0	161.0	159.7
LDL cholesterol (mg/dL)	82.8	81.2	82.4	83.5	82.0
HDL cholesterol (mg/dL)	44.5	43.7	43.7	44.0	43.7
Triglycerides (mg/dL)	139.0	139.9	139.1	138.2	139.1
eGFR (mL/min/1.73m^2)	79.0	79.0	79.0	78.0	78.5
Loss to follow-up N, (%)	9 (0.27)	9 (0.41)	5 (0.22)	4 (0.18)	18 (0.27)

STEMI= ST elevation myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary bypass graft surgery; hsCRP=high sensitivity C-reactive protein; HDL=high density lipoprotein cholesterol; LDL=low density lipoprotein cholesterol; eGFR=estimated glomerular filtration rate

* Beta-blocking agents, nitrates, or calcium channel blocking agents

Median values are presented for all measured plasma variables, body mass index and waist circumference

D. Supplemental Table S2. Incidence rates (per 100 person years) and hazard ratios for lung cancers among current and past smokers.

		Canakinumab Dose (SC q 3 months)				
	Placebo (N=3344)	50mg (N=2170)	150mg (N=2284)	300mg (N=2263)	All Doses (N=6717)	P-value for trend across doses
Lung Cancer, Current Smokers						
Incident rate, (N)	0.97 (28)	0.46 (9)	0.75 (15)	0.25 (5)	0.49 (29)	0.0055
Hazard ratio	1.00	0.49	0.76	0.25	0.50	
95 % CI	(referent)	0.23-1.05	0.40-1.42	0.10-0.65	0.30-0.84	
P	(referent)	0.06	0.38	0.0022	0.0073	
Lung Cancer, Past Smokers						
Incidence rate, (N)	0.51 (31)	0.48 (18)	0.25 (10)	0.23 (9)	0.31 (37)	0.0064
Hazard ratio	1.00	0.95	0.48	0.44	0.61	
95% CI	(referent)	0.53-1.71	0.24-0.99	0.21-0.92	0.38-0.99	
P	(referent)	0.87	0.0412	0.0254	0.0435	

E. Supplemental Table S3. Incidence rates per 100 person years and (number) for lung cancer types and other site-specific non-lung cancers in CANTOS.

Cancer Site or Type	Placebo (N=3344)	Canakinumab Dose (SC q 3 months) 50mg (N=2170)	150mg (N=2284)	300mg (N=2263)	All Doses (N=6717)	P-value for trend across doses	P-value for combined dose groups
Lung Cancers							
Adenocarcinoma or poorly differentiated large cell carcinoma or unspecified	0.41 (52)	0.33 (26)	0.27 (23)	0.12 (10)	0.23 (59)	<0.0001	0.0022
Squamous cell lung carcinoma	0.03 (4)	0.01 (1)	0.02 (2)	0.03 (3)	0.02 (6)	0.74	0.65
Small cell lung cancer	0.04 (5)	0.01 (1)	0.01 (1)	0.01 (1)	0.01 (3)	NA	NA
Pleural cancer	0.01(1)	0	0	0	0	NA	NA
Other Cancer Sites							
Skin							
Basal cell carcinoma	0.18(23)	0.28(22)	0.29(25)	0.21(18)	0.26(65)	0.80	0.16
Squamous cell skin cancer	0.16(20)	0.10(8)	0.15(13)	0.27(23)	0.17(44)	0.0356	0.74
Melanoma	0.02(3)	0.08(6)	0.06(5)	0.06(5)	0.06(16)	0.44	0.11
Other	0.06(8)	0	0.06(5)	0.02(2)	0.03(7)	0.41	0.10
Gastrointenstinal							
Oral cavity/tongue	0.02(3)	0.03(2)	0.05(4)	0.02(2)	0.03(8)	0.98	0.69
Esophageal	0.06(8)	0.08(6)	0.03(3)	0.08(7)	0.06(16)	0.80	1.00
Gastric	0.08(10)	0.04(3)	0.02(2)	0.06(5)	0.04(10)	0.54	0.11
Colorectal	0.16(20)	0.25(20)	0.19(16)	0.21(18)	0.21(54)	0.66	0.26
Biliary	0.01(1)	0.03(2)	0.03(3)	0	0.02(5)	NA	NA
Appendiceal	0.01(1)	0	0	0.01(1)	0.00(1)	NA	NA
Pancreatic	0.06(8)	0.04(3)	0.06(5)	0.06(5)	0.05(13)	0.95	0.64
Hematopoetic							
Lymphoma	0.06(7)	0.04(3)	0.05(4)	0.07(6)	0.05(13)	0.57	0.87
Leukemia	0.01(1)	0.01(1)	0.02(2)	0.01(1)	0.02(4)	NA	NA
Multiple myeloma	0.02(2)	0	0	0.02(2)	0.01(2)	NA	NA
Endocrine							
Thyroid	0.03(4)	0.01(1)	0.02(2)	0.01(1)	0.02(4)	NA	NA
Adrenal	0.02(2)	0	0.01(1)	0.01(1)	0.01(2)	NA	NA
Genitourinary							
Bladder	0.06(8)	0.10(8)	0.08(7)	0.13(11)	0.10(26)	0.21	0.23
Prostate	0.15(19)	0.19(15)	0.16(14)	0.17(15)	0.17(44)	0.85	0.60
Testicular	0	0	0.01(1)	0	0.00(1)	NA	NA
Ovarian	0	0	0	0.01(1)	0.00(1)	NA	NA
Endometrial/Uterine	0.01(1)	0.03(2)	0	0.03(3)	0.02(5)	NA	NA
Cervical	0.01(1)	0	0.01(1)	0	0.00(1)	NA	NA
Breast	0.06(8)	0.09(7)	0.05(4)	0.06(5)	0.06(16)	0.63	0.99
Kidney	0.06(8)	0.13(10)	0.07(6)	0.07(6)	0.09(22)	0.77	0.44
Liver	0.07(9)	0.04(3)	0.06(5)	0.03(3)	0.04(11)	0.38	0.26
Central Nervous System	0.01(1)	0.04(3)	0.05(4)	0.03(3)	0.04(10)	0.32	0.09
Sarcoma / Bone	0.03(4)	0.01(1)	0	0.01(1)	0.01(2)	NA	NA
Other	0.09(11)	0.08(6)	0.06(5)	0.02(2)	0.05(13)	0.0472	0.19

NA – tests for significance not performed if event number < 10.

F. Supplemental Table S4. Sensitivity analysis of incidence rates (per 100 person years) and hazard ratios based upon all reported cancers in CANTOS rather than on adjudicated cancers.

Clinical Outcome	Placebo (N=3344)	Canakinumab Dose (SC q 3 months) 50mg (N=2170)	150mg (N=2284)	300mg (N=2263)	All Doses (N=6717)	P-value for trend across doses
Any Reported Cancer (all)						
Incident rate, (N)	1.94(237)	1.88(146)	1.76(148)	1.80 (150)	1.81(444)	0.41
Hazard ratio	1.00	0.98	0.91	0.93	0.93	
95 % CI	(referent)	0.79-1.20	0.74-1.11	0.76-1.14	0.80-1.09	
P	(referent	0.81	0.35	0.47	0.40	
Any Reported Cancer (fatal)						
Incidence rate, (N)	0.64(81)	0.55(44)	0.50(44)	0.31 (27)	0.45(115)	0.0007
Hazard ratio	1.00	0.86	0.78	0.49	0.71	
95% CI	(referent)	0.59-1.24	0.54-1.13	0.31-0.75	0.53-0.94	
P	(referent)	0.42	0.19	0.0009	0.0158	
Reported Lung Cancer (all)						
Incidence rate, (N)	0.50(62)	0.35 (28)	0.31(27)	0.20 (17)	0.29(72)	0.0003
Hazard ratio	1.00	0.73	0.62	0.39	0.58	
95% CI	(referent)	0.47-1.15	0.40-0.98	0.23-0.67	0.41-0.81	
P	(referent)	0.17	0.0395	0.0004	0.0013	
Reported Lung Cancer (fatal)						
Incidence rate, (N)	0.30(38)	0.20(16)	0.19(17)	0.07(6)	0.15(39)	0.0002
Hazard ratio	1.00	0.67	0.64	0.23	0.51	
95% CI	(referent)	0.37-1.20	0.36-1.14	0.10-0.54	0.33-0.80	
P	(referent)	0.18	0.13	0.0002	0.0026	
Reported Non-Lung Cancer (all)						
Incidence rate, (N)	1.54(189)	1.62(126)	1.53(129)	1.67(140)	1.61(395)	0.55
Hazard ratio	1.00	1.06	0.99	1.09	1.04	
95% CI	(referent)	0.84-1.33	0.79-1.24	0.87-1.35	0.88-1.24	
P	(referent)	0.62	0.94	0.50	0.63	
Reported Non-Lung Cancer (fatal)						
Incidence rate, (N)	0.41(52)	0.40(32)	0.37(32)	0.27(23)	0.34 (87)	0.07
Hazard ratio	1.00	0.97	0.89	0.64	0.83	
95% CI	(referent)	0.63-1.51	0.57-1.38	0.39-1.05	0.59-1.17	
P	(referent)	0.91	0.59	0.08	0.29	